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Immunotherapy of Renal Cell Cancer

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Immunotherapy of metastatic renal adenocarcinoma (RCC) is currently an alternative to cytotoxic chemotherapy. Bacillus Calmette-Guérin has been associated with a 22% response rate in small series, but no large-scale clinical trials have been completed. Transfer factor, in combination with other immunotherapeutic and chemotherapeutic compounds, has a reported 13% incidence of response. Tumor vaccines have caused clinical response in only 5% of patients while monoclonal antibodies have produced partial remission in one of nine patients. Immune RNA has been associated with a 14% overall incidence of response. Tumor necrosis factor has not as yet been studied in any large-scale clinical investigations but preliminary studies are not promising. Leukocyte-derived and recombinant interferons alone have produced responses in 10–20% of patients with tolerable toxicity. Combinations of interferons or with cytotoxic chemotherapy have produced slightly improved responses with short duration and substantial toxicity. Adoptive immunotherapy using Interleukin-2 alone, or with IL-2 plus lymphocyte-activated killer cells, or tumor infiltrating lymphocytes or interferons have produced clinical responses in 10–30% of patients treated. Combinations of specific forms of immune therapy may hold promise for better rates of clinical response in the future.

KEY WORDS: adoptive immunotherapy, interleukin-2, LAK cells, tumor infiltrating lymphocytes, interferons

INTRODUCTION

Advanced renal cell carcinoma (RCC) is not highly responsive to any currently available therapy. Response rates for chemotherapy (primarily vinblastine) are in the range of 15–20%, while hormonal manipulation has only an 8–10% response rate. These poor rates of response have prompted investigation into alternative therapies for this disease, including immunotherapy.

The study of immunotherapy for RCC has been stimulated by the spontaneous regression of metastases from RCC. Freed et al. accumulated 51 cases of idiopathic regression of RCC metastases after nephrectomy [1]. However, many of these cases were not documented histologically and the available data suggest less than a 1% rate of "spontaneous regression" [2]. In 1914, Coley reported mixed results from his treatment of renal tumors with a prolonged course of therapy with a mixture of bacterial toxins [3]. Later investigators reported isolated instances of tumor regression following injection of tumor toxins [4], but only since the 1970s

have there been large-scale investigations of immunotherapy as a treatment modality for advanced RCC.

Strategies for using immunotherapy are either active or passive. Methods of active and passive immunotherapy are listed in Table I. Active immunotherapy attempts to stimulate an immune response to either specific tumor antigens or nonspecific antigens associated with tumor. Active immunotherapy, therefore, requires an intact immune system and an antigen that is recognizable and clearly associated only with tumor. However, the antigenicity of most solid tumors is low, and individual variation between tumors of the same type makes it difficult to isolate a tumor antigen that would be universally recognized and tumor-specific. In addition, there is evidence that patients with cancer have a reduced immune response capacity which diminishes their ability to mount a sufficient immune response [5,6]. As a result

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TABLE I. Immunologic Treatment of Cancer*

Active immunotherapy
Specific
Inactivated tumor vaccines (autologous, allogeneic)
Human tumor hybrids
Monoclonal tumor anti-idiotypic antibodies
Nonspecific
Chemical immunostimulants—levamisole, picabanyl, cimetidine, lysosomes containing macrophage-activating substances
Biological immunostimulants—BCG, cyclophosphamide, <i>C. parvum</i> , etc.
Cytokines—interferon, IL-2, IL-4, tumor necrosis factor (TNF)
Chemotherapy
Passive (adoptive) immunotherapy
Specific
Heterologous antiserum from immunized human monoclonal antibodies—murine, human, chimeric
Biologic—via opsonization, complement fixation, or antibody-dependent cellular cytotoxic mechanisms
Radiotherapeutic—alpha- or gamma-emitting radionuclides
Chemotherapeutic—adriamycin, methotrexate, diphtheria or ricin conjugates
T lymphocytes—autologous, allogeneic, xenogeneic
From in vitro sensitization
From tumor-draining lymph nodes
From TILs
Monoclonal lymphocytes
Allogeneic bone marrow transplants with ablative chemotherapy or radiation therapy (graft versus tumor)
Nonspecific
LAK cells-generated by IL-2
Activated macrophages—interferon
Cytostatic or cytotoxic cytokines—interferon, TNF

*Adapted from Lotze MT, Rosenberg SA [76], with permission from J. P. Lippincott Company.

BCG = bacillus Calmette Guérin; TIL = tumor-infiltrating lymphocyte; LAK = lymphokine-activated killer; IL-2 = interleukin-2; IL-4 = interleukin-4; TNF = tumor necrosis factor.

most efforts have focused on passive immunotherapy. Passive immunotherapy attempts to transfer sensitized immune factors that are either specific or nonspecific to the tumor antigen.

MATERIALS AND METHODS OF ACTIVE IMMUNOTHERAPY Bacillus Calmette-Guérin

Bacillus Calmette-Guérin (BCG) was initially isolated from *Mycobacterium bovis* as an attenuated species for use as a vaccine against tuberculosis. Its antitumor activity has been observed in vivo in studies of tumor growth. Its activity probably principally involves a T-

cell-mediated immune response [7], although there is evidence that it exerts an independent effect on tumor necrosis factor [8].

The results of clinical trials of BCG in renal carcinoma are summarized in Table II. Morales and Eidinger administered subcutaneous BCG to ten patients with metastatic renal carcinoma and achieved objective improvement in five, although only one of these responses met present oncologic criteria for a partial remission [9]. Minton treated nine patients with pulmonary metastases with BCG and achieved an objective response in four [10]. Four patients treated by other investigators did not respond to BCG therapy for their disseminated renal carcinoma [11]. Data on BCG treatment of renal carcinoma

TABLE II. Clinical Trials of Active Immunotherapeutic Agents in Renal Carcinoma*

First author, year	Preparation used	n	CR	PR	Response %
BCG					
Morales, 1976 [9]	1 mg-40 mg BCG	10	0	1	10
Minton, 1976 [10]	Not available	9	0	4	44
Montie, 1982 [11]	5×10^8 organisms, Tia	4	0	0	0
Transfer factor					
Montie, 1977 [13]	Transfer factor alone	10	0	0	0
Montie, 1982 [11]	TF + BCG ± CCNU	21	3	1	19
Tumor vaccines					
Niedhart, 1980 [15]	Tumor + tuberculin/phytohemagglutinin	30	0	2	13
Sahasrabudhe, 1986 [14]	Tumor + <i>C. parvum</i>	48	0	2	4

*TF = transfer factor; CCNU = cyclohexylchloroethylnitrosurea.

is sparse, since there are no randomized large-scale studies of this therapy.

Transfer Factor

Transfer factor is a dialyzable polypeptide derived from lymphocytes that initiates cellular immunity by converting lymphocytes to an antigen responsive state [12]. Montie et al. treated ten RCC patients with transfer factor and achieved stabilization of disease in all patients [13]. An additional cohort of 21 patients treated with either transfer factor alone, or transfer factor with BCG or chemotherapy, achieved a total of three complete remissions and one partial remission [11] (Table II).

Tumor Vaccines

Tumor vaccines are another variation of nonspecific therapy. In this type of therapy, patients are given an intradermal injection of a nonspecific adjuvant plus autologous tumor cells with the intent of exposing the effector cells of the immune system to a higher dose of tumor antigens. In one such study using irradiated tumor cells mixed with *Corynebacterium parvum*, Sahasrabudhe et al. reported two partial remissions and no complete remissions among 48 patients with metastatic renal carcinoma [14]. Other investigators using aggregated tumor adjuvant consisting of autologous tumor cells with tuberculin or phytohemagglutinin have reported a 13% response rate and a 22 week mean duration in 30 patients studied with advanced renal tumors [15] (Table II).

METHODS OF PASSIVE IMMUNOTHERAPY

Monoclonal Antibodies

Kohler and Milstein first produced monoclonal antibodies (mAbs) after hybridization between a malignant myeloma cell line and spleen cells from a mouse immunized against a specific antigen [16]. Since that time, attempts have been made to define mAbs use in the diagnosis and treatment of many tumors. They have been principally used conjugated to radioisotopes for diagnosis and localization of renal tumors. Their use in treatment is much less well defined. Although some researchers have used human mAbs for treatment of non-urollogic malignancies, clinical trials of mAbs in renal carcinoma have been performed with murine and anti-human mAbs

only. Lange et al. reported tumor regression with ¹³¹I-labeled AFP-22 mAbs in mice [17]. Real and associates, using ¹³¹I-labeled mouse F23 mAbs in nine patients with renal carcinoma metastatic to bone reported one partial remission and two mixed antitumor responses (Table III) [18].

Several problems are inherent in the use of mAbs in tumor therapy. First, since tumors are heterogeneous they may require more than one antibody to treat a patient's entire tumor burden. It is possible to create a mixture of multiple mAbs but this involves an increased risk of toxicity and significantly greater expense. In addition, patients exposed to murine mAbs develop anti-mouse antibodies after a single exposure. This limits the effectiveness of mAbs in a patient requiring multiple treatments.

Immune RNA

Therapy with xenogeneic immune RNA involves priming the patient's monocytes with RNA from sheep immunized with either autologous or allogeneic renal carcinoma. Clinical experience with this form of treatment is summarized in Table III. After injection of immune RNA in 20 patients, Ramming and deKernion reported minor responses but no partial or complete remissions in any patient [19]. Richie and colleagues incubated autologous lymphocytes with immune RNA and reinfused the primed cells into 22 patients with metastatic RCC. They reported one complete remission and five partial remissions in their series with all responses of at least 6 months duration [20].

Tumor Necrosis Factor

Tumor necrosis factor (TNF-A), known also as "cachectin," is a secretory protein of macrophages following stimulation by lipopolysaccharide or endotoxin. It is structurally and biologically similar to another cytokine, lymphotoxin (TNF-B), and they may compete for a common receptor. Tumor necrosis factor has been identified as the agent promoting tumor necrosis in endotoxemic mice [21]. Its effect probably involves direct cytotoxicity mediated by a TNF receptor [22], as well as indirect injury to tumor vasculature, causing occlusion of tumor blood vessels [23]. Blick and colleagues reported

TABLE III. Clinical Trials of Passive Immunotherapeutic Agents in Renal Carcinoma

First author, year	n	CR	PR	Response %
Monoclonal antibodies				
Real, 1987 [18]	9	0	1	11
Immune RNA				
Ramming, 1977 [19]	21	0	0	0
Richie, 1984 [20]	22	1	5	27
Tumor necrosis factor				
Blick, 1987 [24]	2	0	1	50

a series of patients with various carcinomas given TNF, including two patients with disseminated renal carcinoma of which one had a partial remission. Toxicities involved a flu-like syndrome with fever and chills [24]. More recently, Burgers et al. reported a synergistic effect of TNF and VP-16 in mice with metastatic renal carcinoma. They speculated that this synergism may have been due to targeted destruction of DNA [25]. To date, however, TNF has not demonstrated substantive antitumor effect in any cancer in clinical trials.

Interferons

Interferons are cytokines with a broad spectrum of biological activities. There are three main types of interferons. Alpha interferon is leukocyte-derived, while beta interferon is fibroblast-derived; these interferons share the same receptor [25]. Gamma interferon, or immune interferon, is structurally distinct and shares only the antiviral properties of the other interferons. Their exact physiologic roles are unclear, and the precise mechanism of their antitumor effect has not been defined. They appear to interfere with viral protein synthesis and may inhibit tumor protein synthesis as well, as evidenced by the fact that the fraction of cells in the G₀ phase of the cell cycle is increased in cells treated with interferons [26].

In addition, interferons affect the immune system by augmentation of natural killer (NK) cell activity [27,28]. They also appear to stimulate the expression of class I major histocompatibility complex (MHC) gene products [29] as well as beta-2 microglobulin [30]. Gamma interferon also stimulates the expression of class II MHC gene products [31].

Quesada and colleagues reported the first trial of leukocyte alpha interferon in disseminated renal carcinoma [32] (Table IV). Nineteen patients with advanced RCC were given partially purified leukocyte alpha interferon at 3 million units per day by IM injection. Five of these patients showed a partial remission with two other patients obtaining a minor response. Numerous other studies have been done with both partially purified and re-

combinant interferons [33-35]. These studies have shown response rates ranging from 0 to 50%, with a median response rate of 13%. These studies are summarized in Tables IV through VII. Comparison of these studies illustrates that there is not a significant difference in response rates between the various subtypes of alpha interferon, whether from human or recombinant sources. Overall response was 19% for human leukocyte interferon, 17% for partially purified leukocyte interferon, and 14% for recombinant alpha interferons. In addition, it is clear from the few reported trials (Table VI, VII) that beta and gamma interferons do not have significantly more antitumor activity than does alpha interferon.

Those studies, in which different doses of interferons were used, suggest that higher doses are associated with greater response. Kirkwood et al. found no remissions in a group of 14 patients randomized to 1 million units per day, while 3 of 16 patients responded at 10 million units per day [36]. Similarly, Quesada found no responses in 15 patients given 2 million units per day of alpha-2 interferon, while 4 of 15 patients given 20 million units per day had partial remission [37].

The role of anti-interferon antibody in the clinical response to interferon therapy is not clear. Quesada noted antibodies in 30% of patients treated with recombinant alpha-2 interferon; development of these antibodies, however, did not affect response or patient survival [37]. In addition, Muss et al. observed the development of antibodies to alpha-2 interferon in 7 of 131 patients, of which 3 were responders. The presence of the antibodies did not affect the rate or duration of response or the toxicity [38]. However, there have been other reports of patients whose responses seem shortened by the development of anti-interferon antibodies [39].

Combinations of alpha interferon with chemotherapeutic agents (notably vinblastine) have not, in general, demonstrated substantial improvement in response rates over interferon alone [39]. Neidhart demonstrated no significant difference in the response of recombinant alpha-2 interferon with low-dose vinblastine, but found significant hematologic toxicity and a 10% incidence of death from sepsis at vinblastine doses of 10 mg/m² [40].

TABLE IV. Activity of Partially-Purified Leukocyte Alpha Interferon in Metastatic Renal Carcinoma

First author, year	Dose, route	n	CR	PR	Response %
Quesada, 1983 [32]	3 million units IM	19	0	5	26
deKernion, 1983 [33]	3 million units IM	43	1	6	16
Neidhart, 1984 [34]	5 million units IM	33	0	5	15
Murumo, 1984 [35]	3 million units IM	18	1	0	6
Kirkwood, 1985 [36]	1-10 million units IM	30	1	2	10
Quesada, 1985 [55]	3 million units IM	50	3	10	26
Vugrin, 1985 [56]	3 million units IM	21	0	1	5
Edsmyr, 1985 [57]	3 million units IM	11	1	2	27
					Average 17

TABLE V. Activity of Recombinant Alpha Interferon in Metastatic Renal Carcinoma

First author, year	Dose, route	n	CR	PR	Response %
Alpha-2a					
Krown, 1983 [58]	50 million units IM	19	0	2	11
Quesada, 1985 [37]	2-20 million units IM	30	0	4	13
Taguchi, 1986 [59]	3-50 million units IM	108	2	13	13
Fossa, 1986 [60]	36 million units IM	2	0	1	50
Buzaid, 1987 [61]	3-36 million units IM	22	1	4	22
					Average 15
Alpha-2b					
Umeda, 1986 [38]	6-10 million units IM	45	1	7	18
Muss, 1987 [62]	2 million units SQ	97	2	6	8
					Average 11

TABLE VI. Activity of Recombinant Beta Interferon in Metastatic Renal Carcinoma

First author, year	Dose, route	n	CR	PR	Response %
Kish, 1986 [63]	3-30 million units IV	16	0	1	6
Rinehart, 1986 [64]	.01-60 million units IV	15	0	3	20
					Average 13

Adverse effects of interferons consist of a flu-like syndrome characterized by fever, chills, tachycardia, malaise, and myalgia. The chronic, dose-limiting effects of interferons include fatigue, weakness, and anorexia [41]. These chronic toxicities, unlike the acute effects, do not diminish with continued therapy and represent a notable limitation in view of the poor rate of response.

ADOPTIVE IMMUNOTHERAPY Interleukin-2

Adoptive immunotherapy involves the administration of immune cells that directly or indirectly mediate anti-tumor effects. Interleukin-2 (IL-2), or T-cell growth factor, is a secretory product of activated T-helper lymphocytes and can induce proliferation of human lymphocytes [42]. Of interest is the fact that lymphocytes incubated with IL-2 developed improved cytotoxic activity against a variety of tumors in vitro, and that these cells can lyse tumors in vivo [43]. The cloning and expression of the human IL-2 gene has been accomplished, allowing for production of large quantities of recombinant IL-2 and facilitating its use in non-clinical and clinical trials.

Lymphokine-activated killer (LAK) cells are produced during incubation of lymphocytes with IL-2. They are capable of in vitro lysis of both autologous and allogeneic tumor cells as well as cultured cell lines, including both NK-sensitive and NK-resistant cells, through a non-specific mechanism not linked to MHC antigens. The LAK population is heterogeneous; it includes subpopulations with phenotypic resemblances to T cells, as well as those that resemble NK cells.

A third form of adoptive immunotherapy involves tu-

mor-infiltrating lymphocytes (TILs), which use IL-2-activated and -expanded lymphocytes cultured directly from tumor. This method may allow for lower doses of IL-2 and may increase cytolytic activity per cell. Freshly isolated TILs show only minimal antitumor activity, while those incubated with IL-2 show cytotoxicity against a variety of tumors in vitro using an MHC-specific mechanism [44].

Studies of all these forms of adoptive immunotherapy are listed in Table IX. The results of single-agent IL-2 studies have generally been disappointing. In the NCI surgical branch study, involving 31 patients treated with high-dose interleukin-2, complete remission was noted in only three patients and partial remission in two, representing an overall response rate of only 16% [44]. Other phase I-II studies in renal carcinoma show no response in 14 patients treated with 0.5 to 4 million units/m² of IL-2, although one of four patients treated with intravenous bolus IL-2 achieved a partial remission [45]. Sosman et al., using a low-dose regimen, demonstrated three partial remissions in 17 patients with metastatic renal carcinoma treated with 1 to 3 million units/m²/day for an overall response rate of 18% with less toxicity than reported in the NCI trials [46].

The central role of LAK cells in the cytotoxic effect of IL-2 prompted Rosenberg et al. to administer LAK cells with IL-2 to measure tumor response. This protocol consisted of 5 days of IL-2 (100,000 units/kg every 8 hours), followed by leukopheresis and in vitro expansion of the lymphocytes. These LAK cells were then re-infused in conjunction with 4 to 5 additional days of IL-2. They reported four complete remissions and eight partial remissions in the first 36 patients treated with this regime,

TABLE VII. Activity of Recombinant Gamma Interferon in Metastatic Renal Carcinoma

First author, year	Dose, route	n	CR	PR	Response %
Rinehart, 1986 [65]	.0001-.75 mg/m ² IV	24	0	0	0
Quesada, 1987 [66]	.25-1.0 mg/m ² IM	14	0	1	7
Garnick, 1988 [67]	.01-3.0 mg/m ² IV	40	1	3	10
					Average 6

TABLE VIII. Activity of Interferon and Cytotoxic Chemotherapy in Metastatic Renal Carcinoma

First author, year	Dose, route	n	CR/PR	Response %
Abdi, 1985 [68]	30 million units IFN-B IV 0.2 mg/kg vinblastine	10	0	0
Bergerat, 1985 [69]	10-20 million units INF/A IV 0.075-0.15 mg/kg vinblastine	13	5	38
Figlin, 1985 [70]	3 million units IFN-A IM 0.10-0.15 mg/kg vinblastine	23	3	13
Fossa, 1986 [60]	36 million units IFN-A IM 0.10-0.15 mg/kg vinblastine	16	5	31
				Average 21

TABLE IX. Clinical Trials of Interleukin-2 in Metastatic Renal Carcinoma

First author, year	Dose	n	CR	PR	Response %
IL-2 alone					
Rosenberg, 1984 [71]	0.1 million units/18 h/kg	31	3	2	16
Hemstreet, 1987 [45]	0.5-4.0 million units	14	0	0	0
Whitehead, 1987 [72]	0.5-5.0 million units	14	0	0	0
Sosman, 1988 [46]	1-3 million units	17	0	3	18
Goldstein, 1989 [73]	1 million units	9	0	0	0
Marumo, 1989 [74]	1 million units	11	2	1	27
					Average 11
IL-2 plus LAK					
Rosenberg, 1987 [47]	.1 million units/8 h/kg	36	4	8	33
West, 1987 [49]	.1 million units/kg/8 h	6	0	3	50
Fisher, 1988 [48]	.1 million units/kg/8 h	34	1	4	16
Philip, 1989 [75]	50.6 million unit cumulative dose	19	0	6	32
					Average 27
IL-2 plus interferon					
Krigel, 1988 [51]	5 million units IL-2 6 million units beta-interferon	21	1	5	29
Markowitz, 1989 [52]	2-3 million units IL-2 2-10 million units alpha-interferon	14	1	2	21
					Average 26
TIL					
Kradin, 1989 [54]	1-3 million units IL-2	7	0	2	29

an overall response rate of 33% [47]. The NCI extramural program using the same treatment protocol reported one complete remission and four partial remissions among 34 patients (16%) [48]. West et al. have documented partial remission in three of six patients with renal carcinoma treated with LAK cells plus continuous infusion of IL-2, with less toxicity than the NCI studies [49]. On the other hand, Weiss et al. found no significant difference in toxicity between bolus injection and con-

tinuous infusion of IL-2 [50]. Fisher and colleagues compared the first groups treated in both NCI trials and found that the differences in response rates were likely attributable to differences in tumor burden, metastatic sites, and pretreatment nephrectomy [48]. Duration of response in the initial NCI studies, was a median of 8 months in the complete remissions and 4 months in the partial remissions.

Some investigators have begun clinical trials of com-

binations of IL-2 and interferons (Table IX). Krigel, using recombinant beta-interferon and IL-2, has reported one complete remission and five partial remissions in 21 evaluable patients [51]. Markowitz, using recombinant alpha-2 interferon and IL-2, has observed a 21% response in 14 patients with one complete remission and two partial remissions [52].

The toxicity of IL-2 is significant and includes hypotension, oliguria, azotemia, substantial fluid retention, nausea, vomiting, respiratory distress due to a "capillary leak" syndrome, fever, chills, hepatic dysfunction, and mental status disturbances, all of which are reversible [43]. A significant fraction of patients treated with IL-2 and LAK require admission to the intensive care unit, but mortality from this therapy was only 2% in the NCI trials.

Finally, Belldgrun et al. have shown that TILs cultured with IL-2 caused activation and expansion of these cells. The majority of these cells in renal carcinoma are T-cytotoxic/T-suppressor (CD4+) cells [53]. In addition, recent studies have shown that TIL were therapeutically more potent than IL-2-activated spleen cells in several murine tumor models [44]. Clinical data on TIL are limited, but Kradin et al. achieved a partial remission in two of seven patients with renal carcinoma treated with TIL [54] (Table IX). Several studies are currently in progress but anecdotal reports do not substantiate improved response rates. Current research is directed at determining whether isolation of TILs with cytotoxicity restricted to autologous tumor cells derived from either the tumor or adjacent lymph nodes will prove to be more efficacious. Further studies with regard to where the TIL cells traffic when introduced into the host and whether responses are due to direct effects of the TIL on tumor cells or are indirect via other as yet imprecise mechanisms are in progress.

Other interleukins, especially IL-4, have shown some promise as antitumor therapy. However, investigation of these cytokines is just getting underway, and no clinical trials have as yet been reported.

CONCLUSIONS

The precise role of immunotherapy in renal carcinoma has not been fully established. No methods of treatment have yet had reproducible response rates of more than 10-20%, which is comparable to those for vinblastine chemotherapy. There is clearly an immunological response but today's methods are nonspecific. It is possible that a subgroup of patients can be identified according to tumor burden, metastatic site, and performance status who have higher response rates to immunotherapy. More importantly, ways may be found to stimulate subpopulations of active T cells or macrophages to improve the specificity of the immune response. Perhaps combina-

tions of cytokines will improve response rates of metastatic RCC to immunotherapy. Further efforts are required to more clearly define the role of immunotherapy in the oncologist's armamentarium against renal carcinoma.

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